

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/35220	International filing date (day/month/year) 25 October 2004 (25.10.2004)	Priority date (day/month/year) 24 October 2003 (24.10.2003)
International Patent Classification (IPC) or national classification and IPC IPC: C12N 5/02(2006.01) USPC: 435/377,375		
Applicant CHENG, TAO		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ (sent to the applicant and to the International Bureau) a total of ___ sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application

Date of submission of the demand 25 October 2004 (25.10.2004)	Date of completion of this report 14 September 2006 (14.09.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Michael Wityshyn <i>Janice Ford for</i> Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

- ☒ the international application in the language in which it was filed.
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

- ☒ the international application as originally filed/furnished
- ☒ the description:
pages 1-25 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____
- ☒ the claims:
pages 26-28 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____
- ☒ the drawings:
pages 1/18-18/18 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/35220**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims <u>1-22</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-22</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-22</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-9 and 19-22 are unclear for the reasons set forth under the "Certain Observations;" however, in order to provide compact prosecution the claims have been interpreted to involve down-regulating the intracellular p18^{INK4c} protein level within human stem cells in order to promote self-renewal of the stem cells (i.e. to proliferate stem cells in an undifferentiated state).

Claims 1-22 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest down-regulating p18^{INK4c} expression in order to promote self-renewal of human-compatible stem cells. Prior to the instant application the role of p18^{INK4c} expression in hematopoietic cell proliferation and differentiation was not fully understood; the instant application shows p18^{INK4c} to be a strong inhibitor of stem-cell self-renewal, thus, by down-regulating expression of the protein one can promote self-renewal of stem-cells.

Claims 1-22 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

----- NEW CITATIONS -----

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/US04/35220

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-9 and 19-22 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-9 and 19-22 are indefinite for the following reason(s):

First, it is noted claims 1-9 and 19-22 are directed to methods which involve controlling self-renewal of a population of human-compatible stem cells, yet none of the claims recite or define a positive method step to control the self-renewal of the stem cells. It is noted the specification suggests the intracellular p18 levels can be transiently controlled by inhibiting expression of the gene by adding an inhibitor of the gene, or by inhibiting the promoter of the gene; such positive steps must be claimed to properly define a method.

Second, it is unclear what is meant by controlling the cells "in an intracellular environment substantially free of p18." "Intracellular" is recognized by those of ordinary skill in the art to mean "within the cell", thus the claim does not make sense as to how a population of cells is controlled within a single cell.

Third, the claim fails to recite whether an intracellular environment substantially free of p18 positively or negatively controls self-renewal of the population of 'human-compatible' stem cells; clearly reduction in intracellular p18 only results in unidirectional control. From the specification it appears an intracellular environment substantially free of p18 results in increased self-renewal of said cell population, such must be clear in the claims.

Claims 14-18 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 14-18 are indefinite for the following reason(s): Claims 14-18 are directed to a composition of matter, as defined by claim 10; however, claims 14-18 do not further limit or define the composition of matter, per se, but rather define limitations directed to intended use and methods involving the composition of matter.

Claims 1-22 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-22 are indefinite because the term "p18" is not limited to the CKI p18^{INK4c} protein, but refers to any 18 kDa protein; therefore it is unclear which 18kDa protein applicants are intending to refer to. Applicant must precisely describe the gene they are intending to control.